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Concise Xanthine Synthesis through a Double-Amidination Reaction of a 6-Chlorouracil with Amidines using Base-Metal Catalysis

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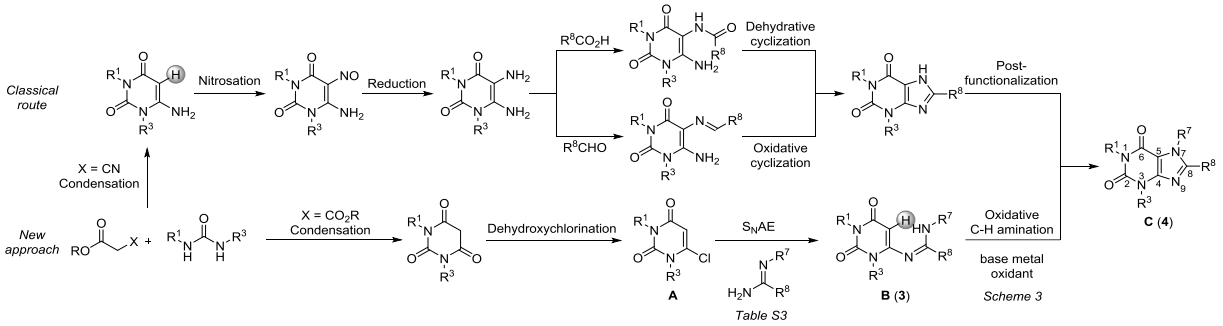
Abstract: A new and concise route towards xanthines through a double-amidination reaction is described; consecutive intermolecular C-Cl and intramolecular oxidative C-H amidination. *N*-uracil amidines are obtained through S_NAE on a 6-chlorouracil with amidines. Direct Cu-catalyzed oxidative C-H amidination on these *N*-uracil amidines yields polysubstituted xanthines. Sustainable oxidants, tBu_2O_2 or O_2, can be used in this oxidase-type reaction. The protocol allows for the introduction of *N*1, *N*3, *N*7, and *C*8 substituents during the xanthine-scaffold construction, thus avoiding post-functionalization steps. Both 6-chlorouracils and amidines are readily available commercially or through synthesis.

Introduction

The purine scaffold is one of the most important heterocyclic motifs and can be considered as a privileged scaffold in medicinal chemistry.[1] Purine derivatives, such as xanthines, display a wide variety of biological activities, and this core can be found in natural products (e.g., caffeine, theobromine) and active pharmaceutical ingredients (e.g., Linagliptin, Dasantafil, Bamifylline, and Istradefylline).[2] The most common way to synthesize xanthines is known as the Traube synthesis (Scheme 1),[3] involving imidazole-ring formation through condensation of a one-carbon fragment (an activated carboxylic acid[4] or an aldehyde[5]) with a 5,6-diaminouracil. The latter is synthesized by nitrosation of a 6-aminouracil followed by reduction. A second general but less frequently applied synthetic approach to xanthines builds up the uracil ring through addition of an alkyl 4-aminoimidazole-5-carboxylate to an isocyanate, which then cyclizes under basic conditions.[6] This route is less attractive because the pre-functionalized imidazole substrate requires a multi-step synthesis. Herein we report a new and general approach towards *N*1-, *N*3-, *N*7-, and *C*8-substituted xanthines, involving two consecutive C-N bond-forming steps starting from readily available *N*1,*N*3-substituted 6-chlorouracils (**A**, Scheme 1). S_NAE of the *C*6 halogen by an amidine leads to an *N*-uracil amidine (**B**), which can be further converted to the corresponding xanthine (**C**) by a direct oxidative amidination reaction.[7] The required amidine reagents can be easily prepared using a Pinner approach, starting from the corresponding nitriles and amines, and allow regioselective installation of R^7 at *N*7.[8,9] In comparison to the Traube synthesis, our approach is shorter, prevents a post-

functionalization step on *N*7 of the xanthine, and avoids a two-step pre-activation, involving nitrosation with unstable nitrous acid and subsequent reduction, at *C*5 of the uracil precursor.[10] These aspects make our approach attractive from a sustainable chemistry point of view.

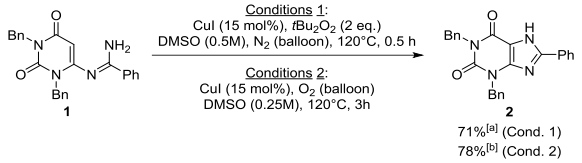


Scheme 1. Classical and new approach for the synthesis of polysubstituted xanthines.

Results and Discussion

Two protocols were developed towards the synthesis of *N*-uracil amidines **3** through S_NAE on 6-chlorouracils (Table S3 in the Supporting Information). The first one requires 2.3 equivalents amidine, acting both as nucleophile and base, in 3-ethyl-3-pentanol at 100°C. The second one uses 1.5 equivalents amidine in combination with 0.7 equivalent 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *tert*-butanol at 80°C. Alcohols as solvent and DBU as a base are preferred from a sustainability point of view.[11] The latter approach is especially interesting for expensive amidines. Interestingly, with *N*-substituted amidines only the unsubstituted nitrogen generally participates in the S_NAE reaction, thus allowing the synthesis of one regioisomer. The target *N*-uracil amidines could often be purified by simple precipitation, avoiding solvent-consuming chromatography on silica gel.

Then, the direct oxidative amidination was investigated. Cross-dehydrogenative C-N bond formation using base-metal catalysis has received considerable attention in the last five years.[12,^13] Only one direct oxidative amination reaction on uracils is hitherto described and reported by our group.[14] In this oxidase-type reaction a stoichiometric oxidant is required. From a sustainability point of view, oxygen and peroxides (H_2O_2 or RO_2R) are the most desirable candidates because the waste compounds are, respectively, water and alcohols.[15] Therefore, these oxidants were considered for the optimization of our cyclization reaction. In a preliminary set of experiments with *N-(*1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzimidamide (**1**) as model substrate, aerobic conditions highlighted CuI as the catalyst of choice (Figure S1). A few other copper sources [$Cu(OAc)_2 \cdot H_2O$, $CuBr_2$, Cu^0 nanoparticles] afforded similar yields of the desired xanthine, but conversion was slower than with CuI (Table S9). Ligands and acids had no or a negative effect on the reaction (Tables S7 and S11, Figure S2). The choice of solvent was critical for the reaction efficiency. Apart from dimethylsulfoxide (DMSO) and tetramethylene sulfoxide, the other solvents tested afforded maximum 15% of reaction product (Table S10). This solvent is well suited from the point of view of health and safety and acceptable with respect to environmental aspects.[16] Using DMSO, full conversion was achieved within 3h using 15mol% CuI at 120°C under O_2 atmosphere. This afforded 1,3-dibenzyl-8-phenylxanthine (**2**) in 78% yield (Scheme 2).[17]



Scheme 2. Direct Cu-catalyzed oxidative C-H amidination of **1** using O_2 or tBu$_2$O$_2$ as oxidant. [a] Isolated yield. [b] NMR yield (1,3,5-trimethoxybenzene as internal standard).

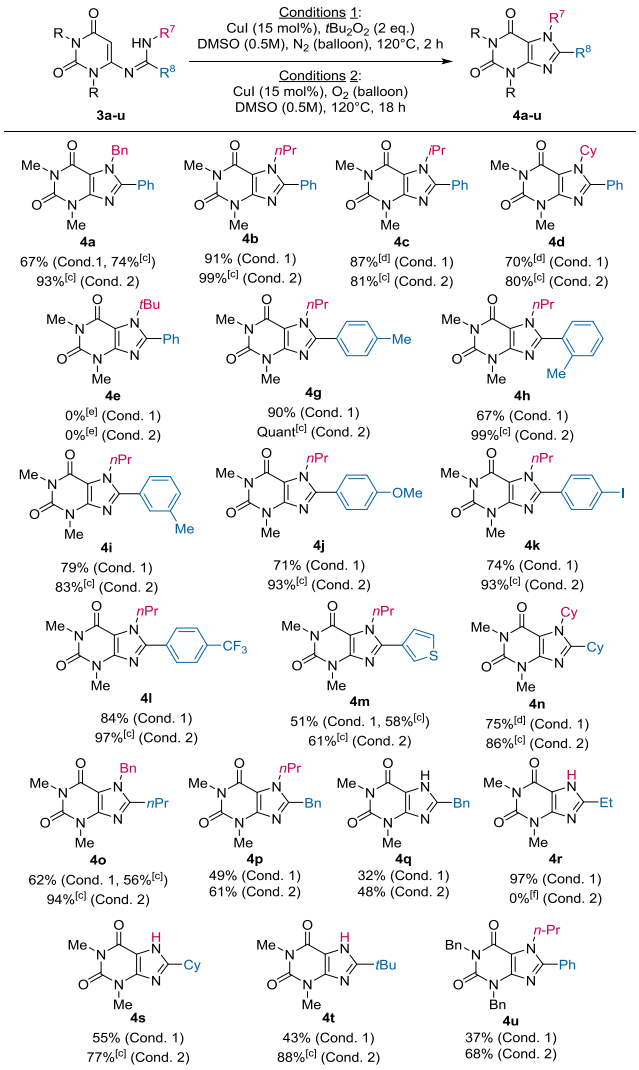
Interestingly, when tBu$_2$O$_2$ was used as the oxidant, **1** was fully converted within 30min and **2** was isolated in 71% yield (Scheme 2). Comparison of the initial rates revealed that the reaction with peroxide was more than ten times faster than with O_2 as oxidant (Figure 1). The specific dialkyl peroxide used is one of the most stable ones, widely used in polymer industry, and only produces *tert*-butanol as waste. Other peroxides afforded a lower yield, and sometimes a low mass balance was obtained (Table S12). Different copper sources were probed using tBu$_2$O$_2$ as the oxidant, but the Cu^{I} and Cu^{II} salts tested were less effective than CuI (Table S14). Other cheap and abundant base-metal catalysts (iron, cobalt, and nickel) were also tried but did not show any reaction (Table S15). Control experiments showed that both catalyst and peroxide were essential because no reaction product was obtained if one of them was omitted (Table S13). Other solvents than DMSO were also explored, such as cyclopentylmethyl ether, 2-methyl-THF, or propylene carbonate.[11b,^11c] Although the latter showed a good mass balance, the yield was low in all cases (Table S16). Therefore, DMSO was retained as the solvent of choice for the transformation.[16] Lowering the reaction temperature to 90°C led to a slower reaction, and full conversion of the substrate required 3h (Figure S5); the use of O_2 at this temperature required 16h. Although the use of a lower temperature is feasible for the direct oxidative amidination reaction, we decided to continue our experiments with 120°C and tBu$_2$O$_2$ as oxidant for the scope study because this combination allowed the fastest reactions. Interestingly, a gradual addition of the peroxide could also be applied, allowing the peroxide concentration to be kept low in the reaction medium (Scheme S3, Figure S3). However, from a practical point of view on a small scale (discovery), we decided not to apply this procedure during the scope study.

We then applied the optimized conditions with tBu$_2$O$_2$ (15mol% CuI and 2 equiv. tBu$_2$O$_2$ in DMSO at 120°C) to a set of synthesized *N*-uracil amidines **3** (Table S3). To our delight, the majority of these substrates were converted into the corresponding xanthines in good-to-excellent yields (Scheme 3). The *N*-uracil benzenecarboximidamide could bear both primary and secondary *N*-alkyl substituents (**3a**-**3d**). The structure of **4b** was confirmed by X-ray crystallography (Figure S8). Only a *tert*-butyl group (**3e**) proved to be incompatible, presumably owing to its steric character. The protocol tolerated a variety of substituents on the aryl ring of the *N*-uracil benzenecarboximidamide, with both electron-donating and electron-withdrawing groups (**3g**-**3l**). Notably, the *para*-iodo-substituted xanthine **4k**, which can be used for further cross-coupling reactions, was obtained in good yield. Because fluorine can have a major influence on the pharmacological properties of a drug,[18] we were pleased to see that our method was also compatible with this halogen (**3l**). *N*-uracil heteroarene-carboximidamide derivatives could also be used as exemplified by **3m**. Even *N*-uracil alkanimidamides were generally well tolerated (**3n**-**3t**), although some of these substrates afforded a lower yield.

O_2 was then tested as alternative oxidant for the substrate scope. Generally, under the optimized conditions (15mol% CuI, with an O_2 balloon, in DMSO at 120°C) higher and in some cases similar

yields were obtained under aerobic conditions, although a much longer reaction time was required (Scheme 3). Again no product could be obtained for **3e**. Remarkably, 1,3-dimethyl-8-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (**4r**) was afforded in 97^% yield using peroxide as oxidant, whereas under aerobic conditions no xanthine was formed. No **3r** was recovered in the latter case and its decomposition mechanism is unclear. **4q** is an intermediate in the synthesis of the active pharmaceutical ingredient Bamifylline.[19] Importantly, irrespective of the oxidant used, several xanthines could be isolated by simple precipitation (**2**, **4a**, **4b**, **4g**, **4j**, **4k**, **4q**).

Scheme 3. Scope of the direct Cu-catalyzed oxidative C-H amidination of *N*-uracil amidines (**3**) using O_2 or tBu_2O_2 as oxidant [a,b].



[a] Cond. 1: **3** (0.5 mmol), CuI (15 mol%), tBu_2O_2 (2 eq.), DMSO (0.5M), 120°C (oil bath), 2 h, closed vial, N_2 atmosphere (balloon). Inert atmosphere is not essential for this reaction but was applied to exclude contribution of O_2 oxidant present in air. Cond. 2: **3** (0.5 mmol), CuI (15 mol%), DMSO (0.5M), 120°C, 18 h, O_2 atmosphere (balloon). Reaction times were not minimized. [b] Isolated yield. [c] NMR yield (1,3,5-trimethoxybenzene as internal standard). [d] 6 h. [e] Only **3e** was detected in the crude reaction mixture via NMR analysis. [f] No **3r** or **4r** were isolated.

Subsequently, we investigated whether the copper catalyst could be reused with model substrate **1**. When adding new substrate and tBu_2O_2 oxidant at the end of the first amidination reaction, full conversion to **2** could again be achieved within 20min in a second reaction (Figure 2). Even a successive four times loading of substrate **1** and tBu_2O_2 resulted in a similar yield (69 vs. 71%) of the

desired xanthine **2**, demonstrating that the copper does not degrade at the end of the reaction (Scheme 4). A similar result was obtained when O_2 was used as the oxidant, affording 65% yield (Scheme 4).

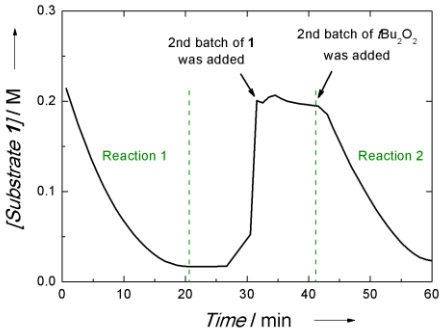
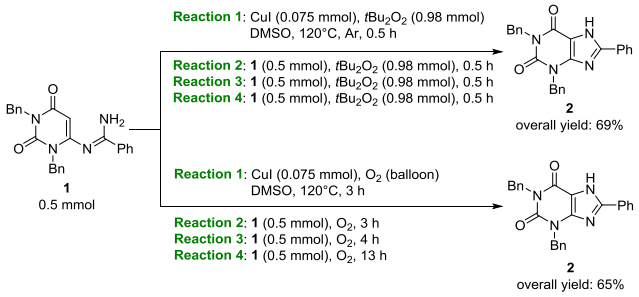


Figure 2. Graphical representation of the reuse of the copper catalyst exemplified for substrate **1** and tBu$_2$O$_2$. After the first reaction was completed, a second batch of **1** and tBu$_2$O$_2$ were added. Conversion was determined by Online IR reaction monitoring.



Scheme 4. Catalyst reuse: experiments with four successive loadings of substrate **1** and oxidant, using tBu$_2$O$_2$ or O_2.

Finally, although our method was designed to install the target substituents at *N*1 and *N*3 when building up the xanthine scaffold, it is also possible to work with *N*-protective groups. 1,3-Dibenzyl-8-phenyl-7-propylxanthine (**3u**), for instance, could be deprotected with BBr_3 in 58% yield using a literature procedure (Scheme S5).[20] This allows post-decoration of the uracil moiety, through *N*-alkylation/arylation or dehydroxychlorination and subsequent consecutive S_NAr, which is especially interesting for medchem purposes.

Conclusions

We have developed a short two-step procedure for the synthesis of polyfunctionalized xanthines starting from readily available 1,3-disubstituted 6-chlorouracils and amidines. S_NAE with amidines afforded the substrates for direct oxidative amidination in moderate-to-good yields. Copper-catalyzed cross-dehydrogenative coupling on these substrates provided *N*1-, *N*3-, *N*7-, and *C*8-substituted xanthines in good yields. Although O_2 led to a significantly slower reaction than tBu$_2$O$_2$ as oxidant for the cross-dehydrogenative C-N bond formation, the former is generally preferred because it affords higher yields. The use of both a readily available and inexpensive base metal (copper) and a sustainable oxidant (O_2 or tBu$_2$O$_2$) makes this protocol valuable for application in both discovery and chemical development projects. Interestingly, in both steps of the new approach,

precipitation of the target compound could often be used for purification, avoiding wasteful column chromatography. The copper catalyst was proven to be reusable, thus further contributing to the sustainability of the new approach.

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Keywords: amidination • base metal • cross dehydrogenative reaction • oxidative C-H amination • xanthines

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